OMICS International
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Peter Nilsson et al., J Proteomics Bioinform 2015, 8:8
http://dx.doi.org/10.4172/0974-276X.S1.076

Neuroproteomic profiling reveals anoctamin 2 as an autoimmune target in multiple sclerosis

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The increasing availability of recombinant components of the human proteome and multiplex array platforms provide unique opportunities for both targeted and discovery-driven analyses of auto-antibody repertoires. We previously identified enriched affinity for 51 out of 11,520 human protein fragments by plasma IgG of individuals with Multiple Sclerosis (MS). Almost all of these antigens were novel auto-antibody targets not previously described in the context of MS. Here, we present an in-depth analysis and further characterization of these previously identified targets together with targets suggested in literature (e.g., KIR4.1) using an independent cohort of 2,169 plasma samples from MS cases and population-based controls on bead-based antigen arrays.We confirmed and strengthened the presence of auto-antibodies against one of our previously proposed targets, a calcium-activated chloride channel protein called Anoctamin 2 (ANO2) in ~15% of MS cases. Here, auto-antibodies against AN02 revealed the most prominent difference within the IgG repertoire between MS cases and controls. These results were reproduced for a subset of samples in independent assays performed at a different laboratory. Using peptide arrays, ANO2 autoantibody epitopes were mapped with higher amino acid resolution. Additionally, we found that the conspicuous HLA complex MS-associated risk genes interacted strongly with the presence of ANO2 auto-antibodies, reinforcing a potential role of the ANO2 auto-reactivity in MS ethiopathogenesis. Further immunofluorescence analysis on human MS brain tissue revealed a clear increase in ANO2 staining as small cellular aggregates near and inside MS lesions. These findings demonstrate the potential for the existence of an ANO2 autoimmune sub-phenotype in MS. They lay the ground for further studies focusing on this particular target with regard to its pathogenic role in MS either directly or as an epiphenomenon.

Biography

Peter Nilsson is a professor in proteomics at the SciLifeLab Stockholm, KTH-Royal Institute of Technology. Since 2002, he has been heading the Protein Microarray Technology group within the Human Protein Atlas project. He is the executive platform director of affinity proteomics at SciLifeLab and the site director of the Human Protein Atlas at SciLifeLab Stockholm. He is also the Vice Dean of the School of Biotechnology at KTH. The main research focus is within development and utilization of various protein microarray technologies for peptide, antigen and antibody based proteomic profiling and biomarker discovery.

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